

REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 17-20 and 22-30 are in the case.

I. ELECTION/RESTRICTION

The election of Group I, namely claims 17-22, is hereby acknowledged. Claims 1-16 have been cancelled without prejudice.

II. THE 35 U.S.C. § 112, FIRST PARAGRAPH, REJECTION

Claims 17-22 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

In response, and without conceding to the merit of this rejection, the claims have been amended to specify GnRH agonist "peptides". The claims as amended are supported by an adequate written description. Thus, the specific exemplification of 5 GnRH agonist peptides in the specification represents a sufficiently "representative number" of examples from the GnRH agonist peptide class to constitute an adequate written description of the invention as now claimed. The specification specifically exemplifies the preparation of implant formulations comprising one of deslorelin, goserelin, leuprolide, buserelin and triptorelin, and provides results obtained from measurement of the scrotal circumference and/or testosterone concentration in dogs administered with such implant formulations.

While the results achieved vary between the different implant formulations, it is clearly demonstrated that **all** achieved **sustained release** of the respective GnRH agonist peptide. From these results, it is clear that the claimed combination of lecithin and stearin is useful for the **class** of GnRH agonist peptides.

In this regard, the class of GnRH agonist peptides is well recognized by persons skilled in the art. As can be seen from the chemical details provided in the specification at page 6, line 21 to page 7, line 14 for seven representative members of the class, GnRH agonist peptides are clearly related. While it is acknowledged that there are structural differences between members of the class, the present Applicants have determined through exemplification that those structural differences are insufficient to thwart the attainment of a **sustained release** profile with an implant formulation of the invention.

Further, in response to the Examiner's comments at the foot of page 4 where he states that there is "substantial variability" between the peptides tested, he speculates that this may lead to "potential inflammatory risks and other unknown physiological effects", and he subsequently queries whether any GnRH agonist peptides would be tolerated *in vivo*, the Applicants are unaware of any particular GnRH agonist peptide being poorly tolerated in humans or other animals. Indeed, it is stated in the highly regarded pharmacological text, Goodman & Gilman's "The pharmacological basis of therapeutics", Tenth edition, at page 1556 (copy attached) that "The long-acting agonists are generally well tolerated, and side effects are those that would be predicted to occur when gonadal steroidogenesis is inhibited (e.g., hot flushes, vaginal dryness and atrophy, decreased bone density)".

In light of the above, it is clear that the Examiner's concerns that there is "substantial variability" are unfounded. What matters, and what has been shown by the Applicants, is that a **sustained release** profile is achieved by the present invention for the GnRH agonist peptide class, and **not** whether any undesirable clinical effects would be experienced with certain GnRH agonist peptides.

In the light of the above and the examples provided in the specification showing the successful preparation of sustained release implant formulations for each of goserelin, leuprolide, buserelin and triptorelin (in addition to deslorelin), it is clear that the invention as claimed in the amended claims is supported by an adequate written description. Withdrawal of the lack of written description is respectfully requested.

III. THE 35 U.S.C. § 112, FIRST PARAGRAPH, REJECTION

Claims 17-22 stand rejected under 35 U.S.C. § 112, first paragraph, on alleged lack of enablement grounds. The Examiner suggests that the specification, while being enabling for five GnRH peptide agonists, does not reasonably provide enablement for any GnRH agonists or GnRH peptide agonist. This rejection is respectfully traversed.

The specification does provide an enabling disclosure with respect to the implant formulation as now claimed. The Examiner's comments regarding concerns that the implant formulations may induce inflammation are misdirected, and appear to constitute a disguised "utility" rejection. Moreover, the Examiner's arguments that there would have been undue experimentation involved in determining whether a particular GnRH agonist peptide may be successfully used in an implant formulation according to the invention is unfounded, and ignores what was known of these compounds by persons skilled in the art. For example, Table 56-3 on page 1553 of the Goodman & Gilman text

(copy attached) lists a number of familiar GnRH agonist peptides and their properties. Again, reference may be made to page 1556 of the Goodman & Gilman text where it is indicated that GnRH agonist peptides have been used, for long periods, in treating children with precocious puberty (nb the reference to "chronic administration"), hormonally-responsive tumours and conditions (*nb*: the reference to depot administration of goserelin). Numerous other clinical applications and studies of GnRH agonist peptides are also referred to in the specification (see, in particular, page 2, lines 3-12 and 22-36, and page 3, lines 1-9 and 15-22). Thus, while experimentation required to determine therapeutic efficacy of a particular implant formulation comprising a GnRH agonist peptide other than one of those specifically exemplified in the specification, may have taken considerable time, the experimentation would **not** be "undue" and, based upon known clinical successes of GnRH agonist peptides, there clearly would have been a "reasonable expectation of success" in the mind of the skilled artisan.

Withdrawal of the outstanding 35 U.S.C. § 112, first paragraph, rejection is now in order. Such action is respectfully requested.

IV. THE 35 U.S.C. § 112, SECOND PARAGRAPH, REJECTION

Claims 17-30 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the reasons described beginning on page 6 of the Action. That rejection is respectfully traversed.

The Examiner contends that it is unclear what is contemplated by the term "at least one GnRH agonist". This claim has now been amended to specify "at least one GnRH agonist **peptide**". In particular, persons skilled in the art can readily identify a

compound as a **peptide analogu** of the peptide GnRH, and also readily test whether such a peptide analogue functions as a GnRH agonist (e.g., by assessing binding and activation of the peptide analogue to the GnRH receptor on gonadotrope cells).

Withdrawal of the outstanding 35 U.S.C. § 112, second paragraph, rejection is now believed to be in order. Such action is respectfully requested.

V. **THE OBVIOUSNESS REJECTION**

Claims 17-22 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent 5,573,781 to Brown et al. That rejection is respectfully traversed.

As claimed, there is provided a pharmaceutical and/or veterinary solid implant formulation comprising about 2-15% (w/w) of at least one GnRH agonist peptide (on an active basis), about 0.5-3.5% (w/w) lecithin, and the balance stearin. The GnRH agonist peptide is other than deslorelin.

There is no disclosure or suggestion in Brown that the pharmaceutical sem-solid would necessarily be suitable for peptide release, nor whether it is appropriate for **sustained release of a peptide**. In particular, the Examiner's attention is directed to column 6, lines 49-52 where it is suggested that the release profile of the cytostatic agent is considerably shorter than that which is achieved by the present invention and, further, that it is the intention of the disclosed pharmaceutical semi-solid that the sustained release profile be of the order of around 6 hours.

Moreover, although the Examiner alleges that the constituents of the present invention are disclosed, flutamide (eulexin) is only one of a **large** choice of possible constituents recited in the specification. In addition, the **broad class** of phospholipids (as opposed to the **specific** phospholipid, **lecithin**) is indicated as one of a large

number of possible "effectors". Accordingly, there is nothing in Brown et al which suggests the specific selection of lecithin, stearin and a GnRH peptide agonist (e.g., eulexin) or the proportions of these components indicated in the present claims.

In light of the above, it is clear that one of ordinary skill would not have been motivated to arrive at the presently claimed invention based on Brown. Absent any such motivation, it is clear that Brown does not give rise to a *prima facie* case of obviousness. Reconsideration and withdrawal of the outstanding obviousness rejection are accordingly respectfully requested.

VI. DOUBLE PATENTING

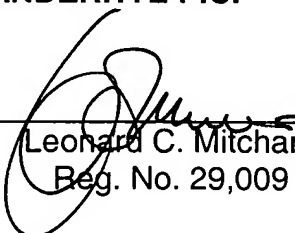
The claims in the present application have been amended so as to be not coextensive with claims 1-10 of parent U.S. Patent No. 6,337,318. Withdrawal of the double patenting rejection is accordingly respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____


Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100
Attachment: Goodman & Gilman's "The pharmacological basis of therapeutics", Tenth edition, pages 1553 and 1556

Table 55-3
Structures and Relative Potencies of GnRH and GnRH Analogs

NAME	RELATIVE POTENCY	AMINO ACID SEQUENCE										DOSAGE FORM
		1	2	3	4	5	6	7	8	9	10	
GnRH (FACTREL, LUTERELSE)	1	PyroGlu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly-NH ₂	IV
Leuprolide (LUPRON)	15						D-Leu				N-EtNH ₂	SC, depot IM
Buserelin (SUPREFACT)	20						D-Ser (tBu)				N-EtNH ₂	SC, IN
Mafarelin (SYNAREL)	150						D-Nal				N-EtNH ₂	SC, IN
Deslorelin	150						D-Trp				N-EtNH ₂	SC, depot IM
Histreltin (SUPPRELIN)	150						D-His (ImBzl)				N-EtNH ₂	SC
Goserelin (ZOLADEX)	100						D-Ser (tBu)				AzGly-NH ₂	Depot SC
Cetorelix (CETROTIDE)	Antagonist	Ac-D-Nal	D-Cpa	D-Pal	Ser	Tyr	D-Cit	Leu	Arg	Pro	D-Ala-NH ₂	SC
Ganirelix (ANTAGON, ORGALUTAN)	Antagonist	Ac-D-Nal	D-Cpa	D-Pal	D-hArg(Et) ²			Leu	hArg(Et) ²	Pro	D-Ala-H ₂	SC

ABBREVIATIONS: Ac, acetyl; N-EtNH₂, N-ethylamide; tBu, t butyl; D-Nal, 3-(2-naphthyl)-D-alanyl; ImBzl, imidobenzyl; Cpa, chlorophenylalanyl; Pal, 3-pyridylalanyl; AzGly, azaglycyl; hArg(Et)², ethyl homocysteine; IV, intravenous; SC, subcutaneous; IN, intranasal; IM, intramuscular.

for either short or long periods—in conjunction with gonadotropins to induce follicular maturation (*see below*)—and then ovulation is induced with CG (Lunenfeld, 1999).

Suppression of Gonadotropin Secretion. As noted above, long-acting GnRH analogs eventually desensitize GnRH receptor-elicited signaling pathways, markedly inhibiting gonadotropin secretion and decreasing the production of gonadal steroids. This “medical castration” has proven to be very useful in disorders that respond to reductions in gonadal steroids. Perhaps the clearest indication for this therapy is in children with gonadotropin-dependent precocious puberty (also called central precocious puberty), whose premature sexual maturation can be arrested with minimal side effects by chronic administration of the GnRH agonists.

Long-acting GnRH agonists are used for palliative therapy of hormonally responsive tumors (*e.g.*, prostate or breast cancer), generally in conjunction with agents that block steroid biosynthesis or action to avoid transient increases in hormone levels. The analogs also are used to suppress steroid-responsive conditions such as endometriosis, uterine leiomyomas, and acute intermittent porphyria. Finally, depot preparations of *goserelin* (ZOLADEX), which can be implanted subcutaneously every 3 months (10.8 mg), may make this drug particularly useful for medical castration in disorders such as pedophilia, where strict patient supervision may be required to ensure compliance.

The long-acting agonists generally are well tolerated, and side effects are those that would be predicted to occur when gonadal steroidogenesis is inhibited (*e.g.*, hot flashes, vaginal dryness and atrophy, decreased bone density). Because of these effects, therapy in settings such as endometriosis or uterine leiomyomas generally is limited to 6 months unless add-back therapy with estrogens is included to minimize effects on bone density.

Diagnostic Uses of Gonadotropins

Diagnosis of Pregnancy. Significant amounts of CG are present in both the maternal bloodstream and urine during pregnancy and can be detected immunologically with antisera raised against its unique β -subunit. This provides the basis for commercial pregnancy kits that qualitatively assay for the presence or absence of CG in the urine. These kits, which offer a rapid, noninvasive means of detecting pregnancy within a few days after a woman's first missed menstrual period, are available in the United States without a prescription.

Quantitative measurements of CG concentration in plasma are determined by radioimmunoassay in clinical and research laboratories. These assays typically are used to assess whether or not pregnancy is proceeding normally or to help detect the presence of an ectopic pregnancy, hydatidiform mole, or choriocarcinoma.

Prediction of Ovulation. Ovulation occurs 36 hours after the onset of the LH surge (10 to 12 hours after the peak of LH). Therefore, urinary concentrations of LH can be used to predict the time of ovulation. Kits are commercially available without a prescription that provide a semiquantitative assessment of LH levels in urine, using LH-specific antibodies that do not recognize other gonadotropins. Urine LH levels are measured every 12 to 24 hours, beginning on day 11 of the menstrual cycle (assuming a 28-day cycle), to detect the rise in LH and thus estimate the time of ovulation. Such estimates facilitate the timing of sexual intercourse to achieve pregnancy.

Diagnosis of Diseases of the Male and Female Reproductive System. Measurements of plasma LH and FSH levels, as determined by quantitative, β subunit-specific radioimmunoassays, are useful in the diagnosis of several reproductive disorders. Low or undetectable levels of LH and FSH are indicative of hypogonadotropic hypogonadism and suggest hypothalamic or pituitary disease, whereas high levels of gonadotropins suggest primary gonadal diseases. Therefore, in cases of amenorrhea in women or delayed puberty in men and women, measurements of plasma gonadotropins can be used to distinguish between gonadal failure and hypothalamic-pituitary failure.

The FSH level on day 3 of the menstrual cycle is useful in assessing relative fertility. An FSH level of ≥ 15 IU/ml is associated with reduced fertility, even if a woman is menstruating normally, and predicts a lower likelihood of success in assisted reproduction techniques such as *in vitro* fertilization (*see below*).

CG also is used diagnostically to stimulate testosterone production and thus assess Leydig cell function in men suspected of having Leydig cell failure (for example, in delayed puberty). Serum testosterone levels are assayed after multiple injections of CG. A diminished testosterone response to CG indicates Leydig cell failure; a normal testosterone response suggests a hypothalamic-pituitary disorder.

Therapeutic Uses of Gonadotropins

Gonadotropins for clinical use originally came from human pituitaries and women's urine. Pituitary extracts